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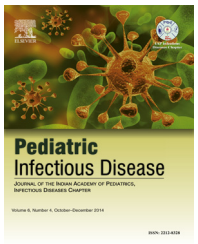

Editorial

Rickettsial diseases in India – A long way ahead...

A surge in the number of publications on this subject from India in recent years and an entire issue of Pediatric Infectious Diseases journal devoted to it, speaks volumes about the burden of rickettsial diseases and its increasing awareness among pediatricians.

There are many paradoxes associated with rickettsial diseases. The first paradox is related to diagnosis and treatment. Rickettsial infections are very difficult to diagnose due to low index of suspicion, nonspecific symptoms and signs, and absence of easily available sensitive and specific tests but these are one of the most easy-to-treat infections having prompt and rapid defervescence with appropriate antibiotics.[1] Second paradox is the cost of diagnosis, vis-á-vis the cost of treatment. While the cost of the definitive diagnosis of rickettsial infections runs into several thousands, the cost of complete treatment with the drug of choice, doxycycline, is meager. Third paradox is about underdiagnosis on the one hand and overtreatment on the other. Rickettsial infections are some of the most underdiagnosed infections, for reasons stated above, in areas where healthcare workers have low index of suspicion; however, in endemic areas, where healthcare workers have high index of suspicion for these infections, most of the patients of undifferentiated fever are irrationally prescribed doxycycline, thanks to the second paradox!

1. Reemerging or endemic...

Epidemiologically, rickettsial infections are prevalent throughout the world, including India. They have been reported from various states and union territories like Maharashtra, Delhi, Karnataka, West Bengal, Pondicherry, Kerala, Tamil Nadu, Himachal Pradesh, Jammu and Kashmir, Rajasthan, and Uttarakhand.[2] Common rickettsial diseases encountered in India are Scrub typhus and Indian tick typhus. For India, these reported numbers are an underestimate due to poor awareness among healthcare professionals, lack of community based data, non-availability of confirmatory laboratory tests, and absence of robust reporting system.[3] Rickettsia are obligate intracellular alpha proteobacteria associated with eukaryotic vectors like blood sucking arthropods (ticks, mites, fleas, and lice). Clinicians do not have access to culture as a diagnostic modality because of the obligate intracellular parasitism of these microorganisms, which prohibit their growth in cell free media and require tissue cultures and laboratory animals for their isolation. Geographic and temporal distribution of vectors decides the epidemiology of rickettsial diseases. Based on lipopolysaccharide group antigen, rickettsia are divided into 4 biogroups, namely spotted fever group (SFG) comprising Rocky Mountain spotted fever, Rickettsialpox, Indian Tick Typhus or Mediterranean spotted fever or Boutonneuse fever; Typhus group comprising Epidemic louse borne typhus, Brill–Zinsser disease and Endemic/Murine flea borne typhus; Scrub typhus group and miscellaneous group comprising Ehrlichiosis, Anaplasmosis, TIBOLA (tickborne lymphadenopathy) and DEBONEL (dermacentor borne necrosis eschar lymphadenopathy). Serological tests are unable to differentiate rickettsia belonging to the same biogroup. Recent use of gene sequencing and genetic phylogeny has led to important changes in the classification of Rickettsiaceae family. All clinical manifestations of rickettsial diseases are explained by infective vasculitis and perivascular inflammatory response leading to occlusion of vascular lumen and vascular leakage. This phenomenon of vascular leakage makes it a differential diagnosis of dengue like illness (DLI). In a large series of rickettsial patients reported in 2011,[4] significant number had received a label of 'DLI' before their definitive diagnosis was made.

2. Clinician's nightmare...

Rickettsial diseases pose multiple problems to the clinician. No symptom or sign is specific enough to make a clinical diagnosis in the initial period, when treatment is going to be highly rewarding. Even with a high index of suspicion, clinician ends up making only an empirical diagnosis as serological tests (ELISA, Microimmunofluorescence), if at all available, become positive about a week after the onset of fever, and specific tests using PCR are not available freely. PCR is a wonderful tool for early diagnosis and can be performed on blood, eschar or skin biopsy samples and more recently eschar swabbing.

An algorithmic or stepwise approach should be used for the diagnosis of rickettsial diseases in a resource poor setting.[1] First step is to keep a high index of suspicion and consider possibility of the rickettsial disease in cases of fever with rash, fever without source, pyrexia of unknown origin, fever with edema, DLI and

acute encephalitic syndrome. Second step is to explore the possibility of vector exposure in the form of tick bite, finding ticks on clothes, history of playing in areas, where ticks are often found in places such as high uncut grass, weeds, low bushes, animal sheds in proximity of homes, contact with pets known to be infested with ticks, travel to endemic areas or occurrence of similar cases simultaneously or sequentially in family members or in the neighborhood. Due to these epidemiological considerations, rickettsial diseases are more common in rural areas, but they are increasingly being reported from urban areas too. Third step is to consider, if clinical features of the index case are compatible with rickettsial disease, e.g. fever, which is high grade, of abrupt onset and associated with headache or myalgia; rash, which appears on day 3–5 of illness, is evolving in nature (progressing from macular to papular to palpable purpura to ecchymotic or gangrenous), involves palms and soles, with centripetal spread; edema, which can be periorbital or generalized and the presence of eschar. A word of caution is necessary about the rash. It could be absent in the beginning or may not appear at all (spotted fever could be spotless too, another paradox!). Fourth step is to see, if the basic laboratory features in the patient are suggestive of rickettsial disease like normal to low total leukocyte count with a shift to left in early stages and leukocytosis later on, thrombocytopenia, raised ESR and CRP, hyponatremia, hypoalbuminemia, and mildly elevated transaminases. Fifth step is to rule out differential diagnoses such as viral infections (dengue, measles, enteroviral diseases, and infectious mononucleosis), bacterial diseases (meningococcemia, typhoid, leptospirosis, and scarlet fever), protozoal diseases such as malaria, vasculitis such as Kawasaki disease, and adverse drug reactions. Last step is to start empirical treatment with doxycycline and send diagnostic tests such as PCR or serological tests (Weil-Felix/ELISA/MIF to be done after 5–7 days of illness), if they are available. Rapid defervescence with doxycycline and/or positive diagnostic tests would establish the diagnosis of rickettsial diseases. The scoring system proposed by Rathi et al. for diagnosis of SFG rickettsioses using clinical, laboratory, and epidemiological features with a diagnostic cutoff score of 14 has high sensitivity (96.1%) and specificity (98.8%), similar to detection of specific IgM antibody by ELISA.[4]

3. Atypical presentations...

Apart from the typical clinical features such as fever, rash, edema, eschar, and hepatosplenomegaly, various atypical presentations deserve special mention. As noted in this issue of PID, neurological presentation is quite common.[5–9] In the article published in this issue,[9] 82% (51/62) of rickettsial diseases in children had neurological manifestations, either at presentation or during the course of their hospitalization, while significant proportion (41%) of rickettsial diseases presented with only neurological manifestation (apart from fever) in the absence of other typical clinical features of these infections. In fact, rickettsial diseases should be considered in the differential diagnosis of every patient with aseptic meningitis or meningoencephalitis or acute encephalitic syndrome in endemic areas with compatible epidemiological history. Unfortunately, many published articles either do not mention this[10] or have recommended diagnostic testing only with history of tick exposure or presence of raised transaminases, but not in relation to geographical region of Asia.[11]

Cough associated with pulmonary infiltrates or pneumonia is another common presentation of rickettsial diseases.[4,12] Indian Council of Medical Research has advised empiric treatment for scrub typhus in addition to recommended regimen for the management of community acquired pneumonia, in regions, where scrub typhus is likely to occur.[13] Adult respiratory distress syndrome (ARDS) is a known complication, occurring in about 5% cases of rickettsial diseases.[4,14] Gastrointestinal and hepatic presentation in the form of nausea, vomiting, diarrhea, abdominal pain, and hepatitis, severe enough to suggest diagnosis of acute gastroenteritis or surgical abdomen, is known in children with rickettsial infections, especially in the early part of the clinical course.[15–18]

Acute renal failure (ARF) can be a presenting feature of rickettsial disease and is associated with a bad prognosis. The possibility of scrub typhus should be borne in mind, whenever a patient of fever presents with varying degrees of renal insufficiency, particularly if eschar exists along with the history of environmental exposure.[19] ARF is reported in 7–19% cases of rickettsial diseases.[4,20]

4. Confirmatory diagnosis: a major challenge in India...

A major challenge in understanding rickettsial epidemiology in India is the lack of widely available confirmatory diagnostic tests. Either detecting rickettsial DNA by PCR or rising antibody titers on acute and convalescent sera detected by Indirect Immune Fluorescence Assay (IFA) or Indirect Immunoperoxidase Assay (IPA) are confirmatory but neither of these tests is available freely in India. Most of the studies in India use a definition of ''probable case'' i.e. a suspected clinical case showing titers of 1:80 or above in OX2, OX19, and OXK antigens by Weil Felix test and an optical density (OD) > 0.5 for IgM by ELISA,[13] but unfortunately even these ELISA tests are not available at most of the centers. Most of the clinicians would rationalize by adding two criteria to a ''probable case'', firstly ruling out the differential diagnoses and secondly, a prompt response to doxycycline, to make a diagnosis. Clinicians, having a high index of suspicion for rickettsial diseases, often circumvent the problem of nonavailability of diagnostic tests by rampant and irrational use of inexpensive and highly effective doxycycline as a therapeutic trial to diagnose this infection. This practice is fraught with high propensity for side effects and more worryingly, drug resistance.

5. Public health impact...

Though in true sense, the public health impact of rickettsial diseases in India largely remains unmeasured (thanks again to a lack of confirmatory tests), but it can be rationally surmised that it is enormous. Public health impact differs in areas where clinicians have a high index of suspicion for these infections and those with low index of suspicion. Vidarbha, a part of central India, is witness to both. Prior to 2010, index of suspicion was low and there was enormous morbidity due to rickettsial diseases in the form of gangrene, neurological sequelae, ARDS, ARF,

gastrointestinal bleed and disseminated intravascular coagulation; high mortality with death rates of 30–35% in untreated cases and huge financial implications for families toward investigations and empiric therapies for these undiagnosed patients. With increasing awareness through IAP meetings, local and regional conferences, local newspapers and publications,[2,4] the index of suspicion for rickettsial diseases is now higher and such severe complications and deaths due to rickettsial diseases are now uncommon. But, on the other hand, there is a rampant overuse of empirical doxycycline therapy now. Ironically, adverse public health impact in both these situations can be significantly reduced by the development of a low cost, rapid and widely available confirmatory diagnostic test.

6. A long way ahead...

Multiple strategies at every level seem to be the answer. Increasing awareness among pediatricians and other primary healthcare professionals is the need of the hour. IAP should take a lead role in the formation of a committee and bring out a consolidated resource material on rickettsial diseases in Indian children. Government should take steps to make health workers at rural hospitals, primary health centers and subcenters aware of clinical and therapeutic approach toward these diseases, as majority of patients are likely to come from there. Finally, the diagnostic tests should be made widely available. At least Weil-Felix and ELISA should be made available at smaller centers while IFA and PCR should be available at metropolitan cities and this strategy should be followed in government as well as private health sectors. Availability of the PCR based diagnostic tests for clinicians will have a distinct advantage for early diagnosis, as serological tests often only help to retrospectively validate the correctness of clinical diagnosis. Research efforts should be directed toward the development of rapid card test, which can have a significant impact. Developing ELISA tests that are agent specific rather than biogroup specific, as is the case presently, would be helpful for epidemiological studies. There is also a need to develop a robust reporting system to gather epidemiological data. Making an intravenous preparation of doxycycline available in India is also an essential step. The government needs to focus on vaccine development, as significant efforts in the past have been in vain.[21]

The pivotal issue is making every pediatrician across the country think about rickettsiosis in appropriate clinical situations, and this is what precisely the present issue of PID intends to do!

Happy Christmas and wish you a great year ahead...

Conflicts of interest

The author has none to declare.

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